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Zonisamide monotherapy with once-daily dosing in children with cryptogenic localization-related epilepsies: clinical effects and pharmacokinetic studies

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KEYWORDS
Zonisamide;
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Monotherapy;
Drug interaction

Summary Clinical effects and pharmacokinetics of once-a-day pediatric zonisamide (ZNS) monotherapy were investigated in 72 children (range, 3 months to 15 years; mean age, 8 years and 3 months) with cryptogenic localization-related epilepsies with simple, complex, or secondarily generalized partial seizures; none had prior epilepsy treatment. ZNS was initiated at 2 mg/kg; daily dosage was doubled at weekly intervals to achieve maintenance dosage (8.0 mg/kg; mean, 7.97 ± 0.55 mg/kg). Blood samples determined trough and peak plasma levels; levels were 27.0 ± 9.4 μg/ml and 33.8 ± 10.8 μg/ml, respectively, with ratios as small as 1.28 ± 0.15. Plasma level to dose ratios increased with age; peak-to-trough ratios were not age variable. Seizures were not controlled in 23 of 72 patients; low trough plasma levels (approximately 15 μg/ml) were observed. Drowsiness/short attention span in five patients instigated a dosage decrease (peak plasma levels >40 μg/ml). During treatment (6–43 months; mean, 27.2 months), seizure control occurred in 57 of 72 patients (79.2%), including eight refractory patients. In 12 patients with uncontrolled seizures and high ZNS levels, carbamazepine (CBZ) was added (BID; mean total dose, 15.1 ± 3.0 mg/kg) to ZNS (QD; mean dose, 11.1 ± 2.5 mg/kg); drug interactions were examined.

Introduction

Zonisamide, an antiepilepsy drug (AED) developed in Japan, was shown to have strong inhibitory effects on convulsions of cortical origin in animal studies by suppressing both focal spiking and the spread of secondarily generalized seizures induced by electric or chemical stimuli.[1,2] Clinical studies have revealed that zonisamide is effective in most types of epileptic seizures, especially for the control of partial seizures.[3–6]

Zonisamide is absorbed slowly from the gastrointestinal tract, and its biological half-life is long compared to other prevalent AEDs. Pilot studies indicate that peak plasma concentrations of zonisamide occur approximately 4 to 6 h after dosing, and that its half-life is long—up to 60 h in adult volunteers.[4,7]

Based on these pharmacokinetic characteristics, we investigated the clinical effects and plasma

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levels of zonisamide in a prospective randomized study where zonisamide was administered once a day as monotherapy to children with cryptogenic localization-related epilepsies.

Materials and methods

Patients comprised 72 children, ages 3 months to 15 years (mean, 8 years and 3 months) with partial seizures, who had not previously received treatment for epilepsy, and were newly referred to our pediatric seizure clinic. All patients were classified as having cryptogenic localization-related epilepsies, and all had experienced two or more seizures before starting zonisamide monotherapy. Four patients had simple partial seizures, 23 had complex partial seizures, and 45 had partial seizures evolving to secondarily generalized seizures (Table 1). No patients showed evidence of mental retardation or other associated neuropsychiatric handicaps.

Patients received zonisamide at a starting daily dose of 2 mg/kg, in order to avoid initial side effects of drowsiness and ataxic gait. The dosage was then doubled at weekly intervals until an initial maintenance daily dose of 8 mg/kg (mean, 7.97 $\pm$ 0.55 mg/kg per day) was reached. Zonisamide was prescribed once a day, in the morning.

Pharmacokinetic data were obtained 4 weeks after starting the maintenance dosage. To determine trough plasma levels of zonisamide in a day, blood samples were taken prior to the morning dose; to determine peak levels, blood samples were taken 4 h after the morning dose. Subsequently, plasma levels were determined every 6 months, and more often as necessary. Determination of plasma levels of zonisamide was performed using high-performance liquid chromatography (HPLC).

Among patients whose seizures could not be controlled by zonisamide monotherapy, even by adjusting dosage and maintaining high plasma levels, carbamazepine was added and drug interactions between zonisamide and CBZ were investigated. The effects of CBZ on seizure control were also observed.

These 12 patients, who were 5 to 16 years old (mean age, 12 years and 1 month), received zonisamide once daily in the morning (mean daily dose, 11.1 $\pm$ 2.5 mg/kg), and CBZ twice daily: once in the morning and once in the evening (mean daily dose, 15.1 $\pm$ 3.0 mg/kg) (Table 2). After combination therapy with zonisamide and CBZ for 6 to 12 months, 9 of the 12 patients discontinued zonisamide, switching to CBZ monotherapy (Table 3). Blood samples for determination of plasma concentrations of zonisamide, CBZ, and its main metabolite, carbamazepine-10,11-epoxide (CBZ-E), were taken before, and 4 h after the morning dose; each represented trough and peak levels of zonisamide and CBZ in a day, respectively. Plasma concentrations of CBZ and CBZ-E were determined by HPLC.

Results

Phase I: clinical effects and plasma levels of zonisamide monotherapy

Initial maintenance daily doses of zonisamide (mean, 7.97 $\pm$ 0.55 mg/kg) yielded trough plasma

Table 1 Patient characteristics.

	Age	
	Mean: 8 years and 3 months	Range: 3 months to 14 years and 11 months
Seizure classification	Simple partial ($n = 4$), complex partial ($n = 23$), simple/complex evolving to secondarily generalized ($n = 45$)	
Initial maintenance dosage	Mea $\pm$ S.D.: 7.97 $\pm$ 0.55 mg/kg per day	Range: 5.82—10.19 mg/kg per day
Duration of follow-up[a]	Mean: 27.2 months	Range: 6—43 months

[a] Excluding 15 cases in whom zonisamide monotherapy was discontinued because of seizure recurrences.

Table 2 Characteristics of patients receiving zonisamide monotherapy, and then zonisamide combined with carbamazepine ($n = 12$).

	Age	
	Mean: 12 years and 1 month	Range: 5—16 years
Dosage (mean $\pm$ S.D.)	ZNS: 11.1 $\pm$ 2.5 mg/kg per day	CBZ: 15.1 $\pm$ 3.0 mg/kg per day

Table 3 Characteristics of patients receiving zonisamide combined with carbamazepine, and then carbamazepine monotherapy ($n = 9$).

	Age	
	Mean: 11 years and 6 months	Range: 5—16 years
Dosage (mean ± S.D.)	ZNS: 11.1 ± 2.8 mg/kg per day	CBZ: 15.8 ± 2.9 mg/kg per day

levels of 27.0 ± 9.4 μg/ml and peak plasma levels of 33.8 ± 10.8 μg/ml. Peak-to-trough plasma level ratios were as small as 1.28 ± 0.15 (Table 4). Ratios of plasma level (μg/ml) to dose (mg/kg per day), estimated by trough and peak plasma levels, increased for both with increasing age (Fig. 1); however, peak-to-trough plasma level ratios were maintained almost uniformly throughout the pediatric age period (Fig. 2).

Clinical effects were then investigated with reference to plasma levels of zonisamide. Of the 72 total patients, seizures were not controlled with the initial maintenance dosage in 23 patients, and recurred within 6 months after administration of zonisamide. Many of the patients who showed low trough plasma levels of zonisamide (approximately 15 μg/ml) had seizure recurrences. In five patients whose peak plasma levels of zonisamide exceeded 40 μg/ml, daily doses were decreased to tolerable levels because of continuous complaints of drowsiness in four patients and short attention span in one patient.

Zonisamide monotherapy was discontinued early in two patients because of frequent seizure recurrences. Dosage increment was difficult in one patient because of the behavioral side effect of short attention span. In one patient whose seizures were not controlled despite high peak plasma levels of zonisamide, CBZ was combined with zonisamide immediately after seizure recurrences. In another patient whose seizures recurred only with fever, rectal diazepam suppositories were given intermittently at the time of febrile illness to control these seizures.

Table 4 Daily fluctuations in plasma zonisamide level in patients receiving zonisamide monotherapy ($n = 72$).

	Plasma level	
	Mean ± S.D.	Range
Trough level (μg/ml)	27.0 ± 9.4	10.2—49.1
Peak level (μg/ml)	33.8 ± 10.8	12.7—65.5
Peak/trough ratio	1.28 ± 0.15	0.98—1.66

In 10 patients whose seizures recurred with the initial maintenance dosage, seizures were not controlled even after increasing the dosage. In eight patients, however, seizure control could be attained by increasing the daily dose of zonisamide, as shown in Fig. 3. This brought the total number of patients whose seizures were controlled on zonisamide monotherapy to 57 of 72 patients (79.2%) over a period of treatment ranging from 6 to 43 months (mean, 27.2 months).

Fig. 4 shows relationships between trough and peak plasma levels of zonisamide at the initial main-

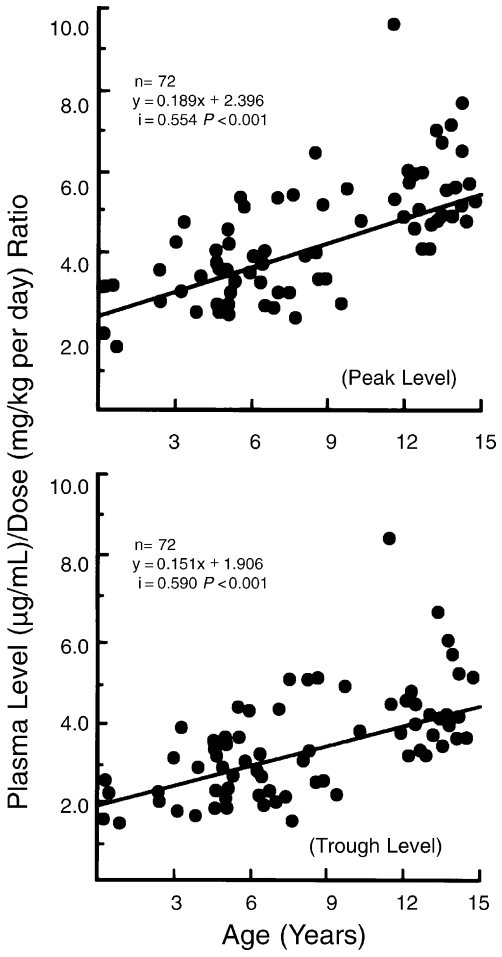

Figure 1 Relationship between age and ratios of plasma level to dose in patients receiving zonisamide monotherapy.

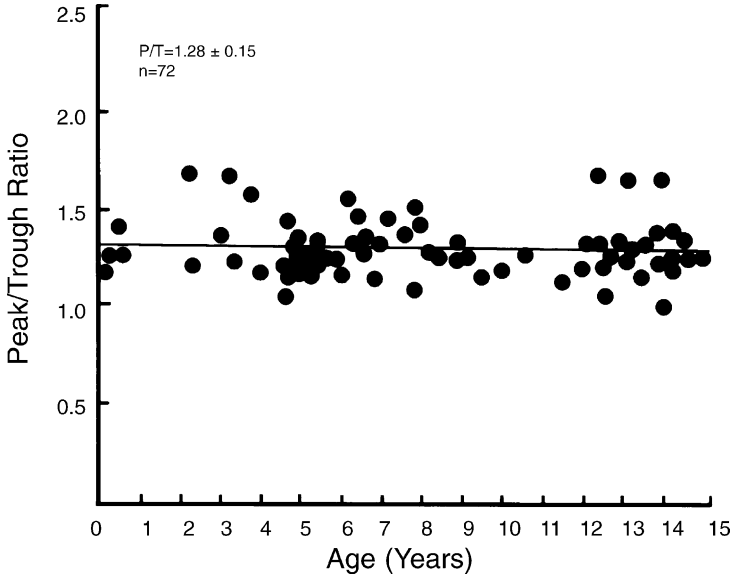

Figure 2 Relationship between age and ratios of peak-to-trough plasma levels in patients receiving zonisamide monotherapy.

tenance dosage, and clinical effects for patients in three age groups (3 months to 6 years, 6 to 12 years, and 12 to 15 years). Generally, plasma levels increased with age, but there was no clear relationship between plasma levels and seizure control in each age group.

Side effects observed with zonisamide treatment included drowsiness (13 patients) and short attention span (2 patients). Most of the adverse effects were transient, but daily doses were decreased to more tolerable levels due to persistent problems with drowsiness in four patients and short attention span in one patient. Loss of appetite appeared transiently in two patients after starting the therapy. In addition, one patient had a rash and agranulocytosis at an early stage of the therapy, and another patient had to be returned to his initial maintenance daily dosage of 4 mg/kg because of continuous complaints of drowsiness; both were excluded from this study. A 6-year-old female patient showed decreased high cerebrocortical activity and mental slowing soon after starting the zonisamide therapy; these complaints disappeared after the therapy was discontinued. This patient was also excluded from the study group.

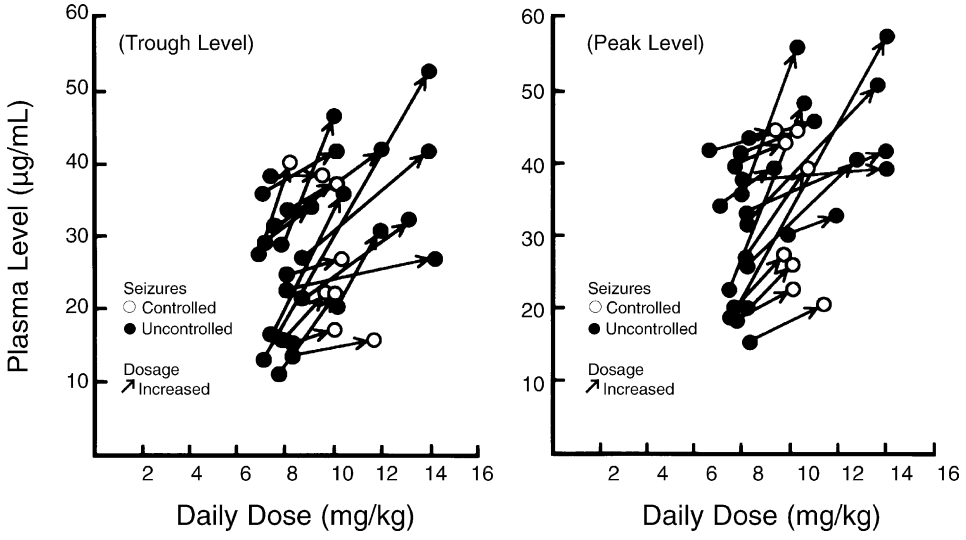

Figure 3 Plasma levels of zonisamide in relation to dosage increases and clinical effects in 18 patients whose seizures were not controlled on initial maintenance dosage.

Table 5 Effect of concurrent administration of carbamazepine on plasma concentrations of zonisamide ($n = 12$).

	Medication	
	ZNS monotherapy	ZNS + CBZ
ZNS trough level (μg/ml)	35.4 ± 10.0	22.2 ± 9.8*
ZNS peak level (μg/ml)	43.0 ± 11.3	28.1 ± 12.5*
Peak/trough ratio	1.23 ± 0.12	1.29 ± 0.22

* $P < 0.05$ (Wilcoxon T).

Phase II: interactions between zonisamide and CBZ

With the addition of CBZ in 12 patients, trough and peak plasma levels of zonisamide decreased from 35.4 ± 10.0 μg/ml to 22.2 ± 9.8 μg/ml, and from 43.0 ± 11.3 μg/ml to 28.1 ± 12.5 μg/ml, respectively (Table 5). Plasma levels of CBZ and CBZ-E before the morning dose were 6.05 ± 1.98 μg/ml and 1.32 ± 0.23 μg/ml, and those 4 h after the morning dose were 9.06 ± 2.83 μg/ml and 1.61 ± 0.35 μg/ml, respectively. Fig. 5 shows the effect of concurrent administration of CBZ on the plasma concentrations of zonisamide in individual patients.

After combination therapy with zonisamide and CBZ, drug therapy was changed to CBZ monother-

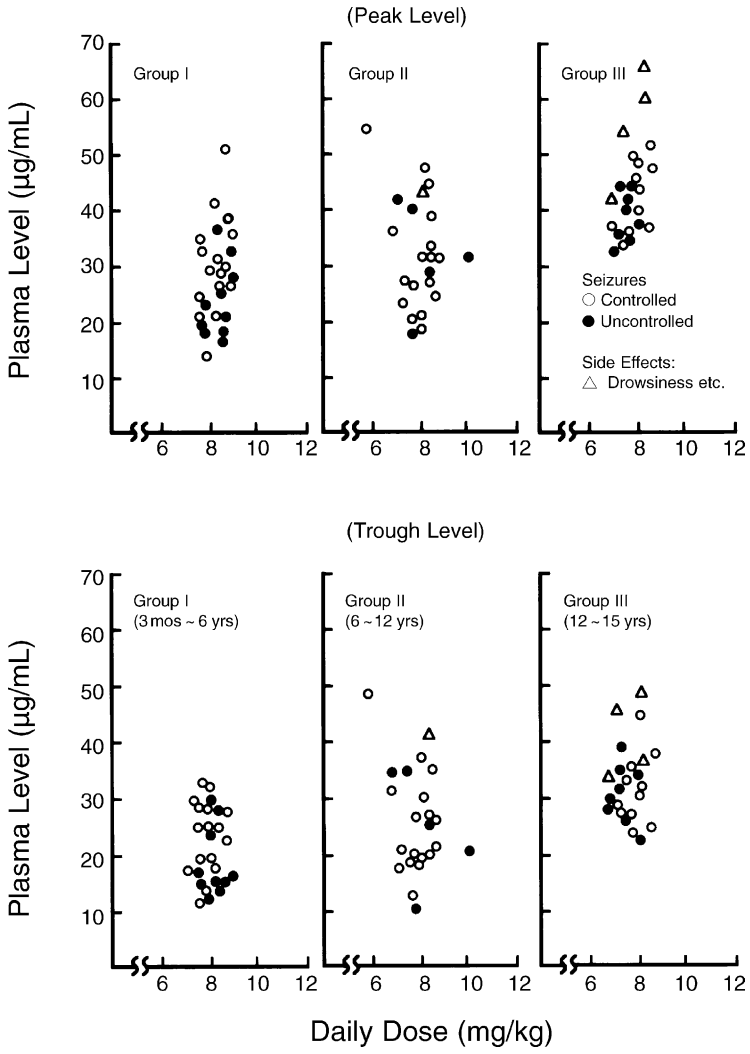

Figure 4 Plasma levels of zonisamide in relation to age and clinical effects on initial maintenance dosage.

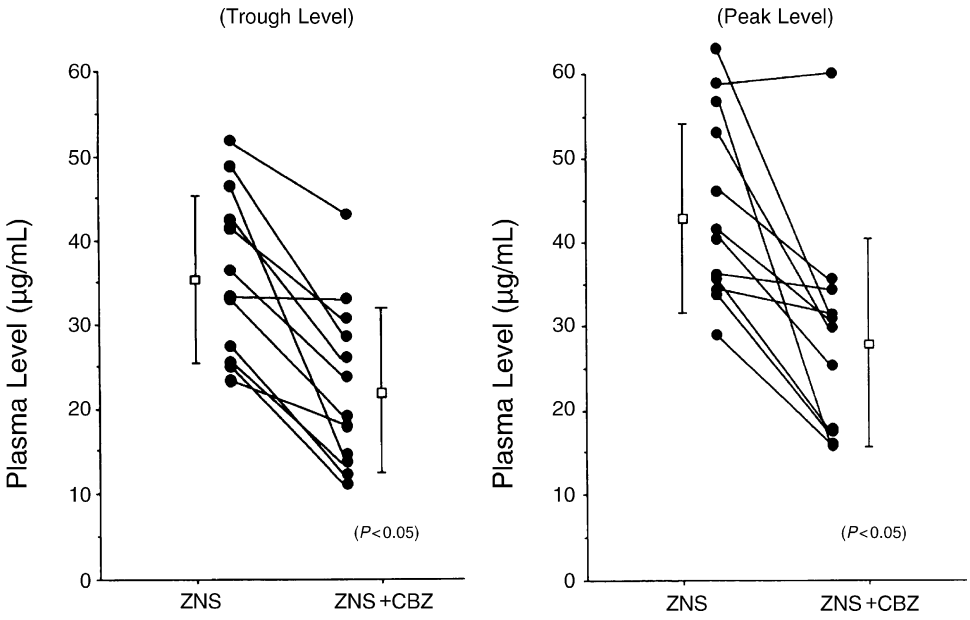

Figure 5 Effect of concurrent administration of carbamazepine on plasma concentrations of zonisamide.

Table 6 Effects of concurrent administration of zonisamide on plasma concentrations of carbamazepine (CBZ) and its epoxide metabolite (CBZ−E) ($n = 9$).

	Medication	
	ZNS + CBZ	CBZ monotherapy
CBZ		
Trough level (μg/ml)[a]	6.05 ± 1.98	6.52 ± 2.06
Peak level (μg/ml)[b]	9.06 ± 2.83	9.24 ± 1.91
Peak/trough ratio	1.52 ± 0.24	1.46 ± 0.23
CBZ-E		
Trough level (μg/ml)[a]	1.32 ± 0.23	1.15 ± 0.19
Peak level (μg/ml)[b]	1.61 ± 0.35	1.50 ± 0.27

[a] Levels before morning dose.
[b] Levels 4 h after morning dose.

apy in 9 of the 12 patients. Comparison of plasma levels of CBZ and CBZ-E in these patients before and after discontinuation of zonisamide revealed no significant differences when CBZ was used alone or in combination with zonisamide (Table 6).

In 6 of the 12 patients whose seizures were not controlled with zonisamide monotherapy, complete seizure control was obtained after addition of CBZ for a period ranging from 7 to 33 months (mean, 24 months). In three of the remaining six patients whose seizures were not controlled with both zonisamide and CBZ, seizures were finally controlled after administration of sodium valproate in two patients, and clonazepam in one patient.

Discussion

Zonisamide is absorbed slowly from the gastrointestinal tract, and its biological half-life is long compared to other common AEDs. Studies[4,7,8] in adult volunteers indicate that the plasma concentration of zonisamide peaks 4 to 6 h after dosing, and that its half-life is as long as 60 h. We investigated the clinical effects and pharmacokinetics of zonisamide given once a day as monotherapy in children with cryptogenic localization-related epilepsies.

In this study, peak-to-trough plasma level ratios during the day were as small as 1.28 ± 0.15 in children taking an initial maintenance daily dose of 8.0 ± 0.6 mg/kg once a day as monother-

apy. This finding was similar to that observed recently in healthy adult volunteers.[8] Plasma level (μg/ml) to dose (mg/kg per day) ratios estimated by trough and peak levels both increased with advancing age, but peak-to-trough plasma level ratios were maintained almost uniformly throughout the pediatric age period. Zonisamide may show nonlinear pharmacokinetics resembling that of phenytoin.[9] This, however, would not be substantiated within the range of generally accepted therapeutic dosage and therapeutic plasma levels.

Although plasma levels varied widely among patients who became seizure free with zonisamide monotherapy, and the final range of plasma levels, after increasing the dosage among patients who did not respond to zonisamide, was high relative to those whose seizures were controlled, the ultimate clinical effects observed were consistent with the range of therapeutic plasma levels generally accepted for zonisamide, that is, 15 to 40 μg/ml.[3,4]

It has been suggested that impairments of high cerebrocortical function, such as decreased spontaneity or memory, are seen in some patients taking zonisamide combined with many other AEDs.[3] However, these adverse effects were not seen in our patients treated with zonisamide monotherapy, except for one patient who was excluded from the study group.

Zonisamide is widely approved as an adjunctive drug for partial seizures. The findings presented here suggest that zonisamide is also effective as monotherapy for partial seizures in children and can provide effective control when taken once daily, which should enhance patient compliance with treatment. However, an initial maintenance dose of zonisamide should be determined based not only on weight but also age, because ratios of plasma zonisamide levels (μg/ml) to dose (mg/kg per day) increase with age.

For patients whose seizures are not controlled by zonisamide, CBZ can be added with some success. Any patient who receives polytherapy is at risk to develop one or more drug interactions. As expected based on zonisamide metabolism by cytochrome P_{450} enzymes, CBZ reduces both peak and trough levels of zonisamide. However, zonisamide does not alter plasma levels of CBZ and CBZ-E. CBZ is extensively metabolized to its active metabolite, CBZ-E, and finally to an inactive metabolite, 10,11-dihydroxycarbamazepine.

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